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(54) Title: SOLID PHASE AND COMBINATORIAL SYNTHESIS OF SUBSTITUTED 1,2,3-TRIAZOLES AND OF ARRAYS OF SUBSTITUTED 1,2,3-TRIAZOLES

(57) Abstract

A solid phase method for the synthesis of a plurality of differently substituted 1,2,3-triazoles with a wide variety of side-chain substituents as compounds of potential therapeutic interest. The 1,2,3-triazoles are prepared by acylation of a substrate-bound primary or secondary amine with a 3-oxoalkanoic acid and reaction of the resulting amide with a primary amine under dehydrating conditions to give an enamine. Treatment of this substrate-bound enamine with a sulfonyl azide in the presence of a base gives the corresponding 1,2,3-triazoles. These may be screened on the substrate or cleaved from the substrate and then screened in solution. The efficient synthesis of a wide variety of 1,2,3-triazoles using automated synthesis technology of the present method makes these compounds attractive candidates for the generation and rapid screening of diverse triazole-based libraries. The method disclosed here provides an easy and fast access to highly diverse heterocyclic compounds of therapeutic interest, amenable to automatization.

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Solid phase and combinatorial synthesis of substituted 1,2,3-triazoles and of arrays of substituted 1,2,3-triazoles

Background of the invention

The present invention relates to the field of solid phase chemistry. More specifically, the invention provides a method for solid phase and combinatorial synthesis of organic compounds, and most particularly, a therapeutically important class of compounds, namely diversely substituted 1,2,3-triazoles.

Obtaining a better understanding of the important factors in molecular recognition in conjunction with developing new therapeutic agents is a major focus of scientific research. Methods have recently been developed, which permit the fast generation of large arrays of pure compounds or of mixtures of compounds, which are then screened against a specific receptor or enzyme. However, there are still only few methods available for the fast synthesis of organic compounds other than peptides or oligonucleotides. The latter tend to have very short clearing times, so that their utility as bioavailable therapeutic agent will be limited. For this reason, organic compounds of potential therapeutic interest are today still synthesized and evaluated one at a time, thus dramatically limiting the number of derivatives which can be screened. It is therefore of utmost importance to develop new synthetic methodology, which permits the fast synthesis of bioavailable organic compounds of potential therapeutic interest, such as small heterocyclic compounds. This may be achieved by developing a solid phase synthesis for such compounds. Experience has shown, that solid phase synthesis, once implemented and optimized, is amenable to automatization and can yield products of high purity without the need of any tedious and time consuming purification step.

The realization of known synthetic reactions on a solid support may not always be possible and may require careful optimization of the reaction conditions. Although solid phase synthesis, once implemented and optimized, offers many advantages if compared to syntheses in liquid phase, the finding of the appropriate reaction conditions may be a difficult task. This may be due to the limited choice of solvents which may be used with some types of supports, as well as the difficulty of precise temperature adjustment in arrays of reactors for solid phase synthesis. Additionally, the classical tools for the quality control of intermediates (infrared spectroscopy, nuclear magnetic resonance spectroscopy, mass spectrometry) may only be of

limited use in solid phase synthesis. For these reasons, the implementation of known reactions to a solid support may often require a major effort and time investment.

The synthetic sequence disclosed in this invention is a variant of related triazole syntheses (ref. 11-19), adapted and optimized for its realization on a solid support.

Terminology

The following terms are intended to have the following, general meanings:

1. Substrate: refers to any insoluble or partially insoluble material, to which compounds may be covalently attached. Substrates may be selected from the group consisting of any kind of organic or inorganic polymeric or oligomeric compound, e.g. polystyrene with different grades of crosslinking, polyethylene glycol (PEG), polyethylene glycol attached to polystyrene (e.g. TentaGel), polyacrylamides, polyamides, polysaccharides or silicates.

2. Linker: a molecule with at least two reactive sites, which permit its covalent attachment to other molecules or to a substrate. Either the bond of the linker to the substrate or the bond of the linker to other molecules attached to it or the linker itself must be cleavable upon selective exposure to an activator such as a selected chemical activator or other specific conditions, e.g. by treatment with a strong acid or by exposure to electromagnetic radiation or by metal catalysis.

3. Array: A collection of N single compounds or N mixtures of compounds with a common structural element, synthesized simultaneously in a parallel fashion using the same synthetic reaction sequence. The precise structure of a single compound within an array of compounds or the components of a mixture within an array of mixtures is determined by the sequence of reactants which gave rise to this specific compound or mixture and can be deduced from the recorded reaction-protocol. The spatial arrangement of the array is irrelevant.

4. Triazole: Five-membered heteroaromatic compound containing three nitrogen-atoms in the five-membered ring.

5. Protecting group: A material which is chemically bound to a molecule or a substrate and which may be removed upon selective exposure to an activator such as a selected chemical activator or other specific conditions, e.g. by treatment with a strong acid or by exposure to electromagnetic radiation or by metal catalysis.

6. Combinatorial synthesis: an ordered strategy for parallel synthesis of arrays of single compounds or mixtures, by sequential addition of reagents.

7. Receptor: A material that has an affinity for a given ligand. Receptors may be naturally-occurring or synthetic molecules or aggregates of molecules. Also, they can be employed in their unaltered state or as aggregates with other species. Receptors may be attached, covalently or non-covalently, to a binding material or a substrate, either directly or via a linking substance. Examples of receptors which can be employed by this invention include, but are not restricted to, antibodies, monoclonal antibodies and antisera reactive with specific antigenic determinants (such as viruses, cells or other materials), cell membrane receptors, drugs, oligonucleotides, polynucleotides, nucleic acids, peptides, cofactors, small organic molecules, lectins, sugars, oligosaccharides, cells, cellular membranes, organelles, microorganism receptors, enzymes, catalytic polypeptides, hormone receptors, primary metabolite receptors such as carbohydrate receptors, nucleotide receptors or lipid receptors and secondary metabolite receptors such as opiate receptors, prostaglandine receptors, etc.

8. Abbreviations: The following frequently used abbreviations are intended to have the following meanings:

AcOH: glacial acetic acid
DCM: dichloromethane, methylenechloride
DMF: N,N-dimethyl formamide
FMoc: fluorenylmethyloxycarbonyl
R: organic radical
TFA: trifluoroacetic acid
THF: tetrahydrofurane
Ts: *p*-toluenesulfonyl

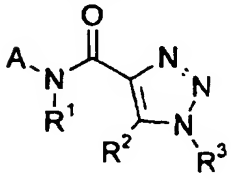
Summary of the invention

An improved method for the synthesis of therapeutically useful compounds is provided by virtue of the present invention. The invention provides a rapid approach for combinatorial synthesis and screening of arrays of triazole derivatives as a therapeutically important class of compounds. It provides a solid phase synthesis of these derivatives, which eliminates purification and isolation steps and thus highly increases synthesis efficiency. This patent disclosure also describes an important extension of solid phase synthesis methods to nonoligomeric organic compounds.

A further understanding of the nature and advantages of the invention may be realized by reference to the remaining portions of the specification.

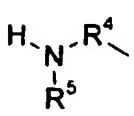
Description

The application of the present invention is the rapid preparation and screening, preferably in parallel and simultaneous fashion, of a large number of differently substituted 1,2,3-triazoles having the general formula I

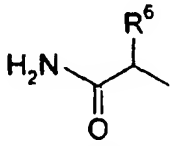


I

wherein A is a hydrogen atom or a group of formula



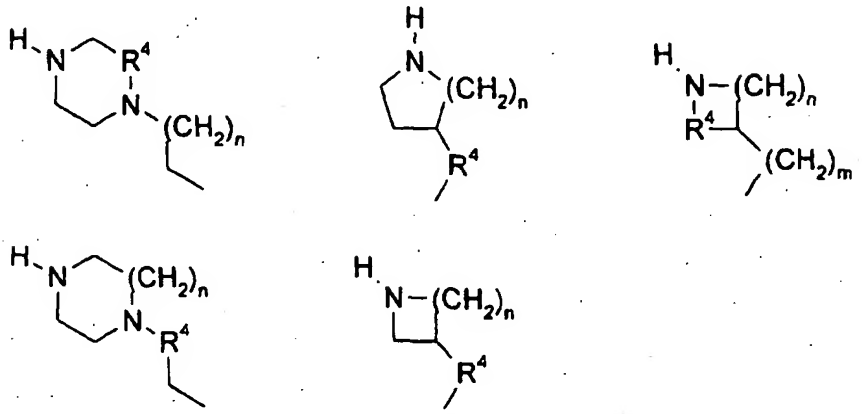
or



wherein R^4 is alkylene optionally substituted with hydrogen, alkyl, aryl, heteroaryl, alkoxy, aryloxy, cyano, hydroxy, dialkylamino, arylalkylamino, diarylamino or halogen;

R^5 is hydrogen, alkyl optionally substituted with hydroxy, halogen, cyano, alkoxy, aryloxy, dialkylamino, arylalkylamino or diarylamino; or aralkyl;

R^4 and R^5 may be covalently linked to each other by a covalent bond or an additional alkylene group R^4, preferentially giving rise to a fragment of the type shown below



wherein n and m are integers between 0 and 15, preferentially 0 and 3;

R^6 is hydrogen, alkyl, alkyl substituted with hydroxy, alkoxy, aryloxy, alkylthio, arylthio, dialkylamino, arylalkylamino or diarylamino; aralkyl, aryl, aryl substituted with alkyl, aryl, heteroaryl, halogen, alkoxy, aryloxy, dialkylamino, alkylarylamino, diarylamino, halogen, cyano, alkoxycarbonyl or aminocarbonyl;

R^1 is hydrogen, alkyl optionally substituted with hydroxy, halogen, cyano, alkoxy, aryloxy, dialkylamino, arylalkylamino or diarylamino; or aralkyl,

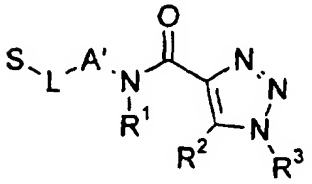
R^1 may be covalently linked to R^4, R^5 and/or R^6, in which case $-R^1-R^4-$ represents low alkylene, preferentially methylene, ethylene or propylene, unsubstituted or substituted with alkyl, hydroxy, alkoxycarbonyl, alkoxy or dialkylamino, $-R^1-R^5-$ represents ethylene or propylene, unsubstituted or substituted with alkyl, hydroxy, alkoxy or dialkylamino, and/or $-R^1-R^6-$ represents methylene, propylene or butylene unsubstituted or substituted with alkyl, hydroxy, alkoxycarbonyl, alkoxy or dialkylamino;

R^2 is alkyl optionally substituted with aryl, heteroaryl, alkoxy, aryloxy, cyano, hydroxy, dialkylamino, arylalkylamino, diarylamino, halogen or aminocarbonyl; aryl optionally substituted with alkyl, aryl, heteroaryl, halogen, alkoxy, aryloxy, dialkylamino, alkylarylamino, diarylamino, halogen, cyano, alkoxycarbonyl or aminocarbonyl; heteroaryl optionally substituted with alkyl, aryl, heteroaryl, halogen,

alkoxy, aryloxy, dialkylamino, alkylarylamino, diarylamino, halogen, cyano, alkoxycarbonyl or aminocarbonyl; and

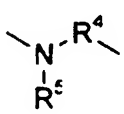
R^3 is alkyl optionally substituted with aryl, heteroaryl, alkoxy, aryloxy, cyano, hydroxy, amino, dialkylamino, arylalkylamino, diarylamino or halogen; and pharmaceutically acceptable salts thereof;

or having the general formula II

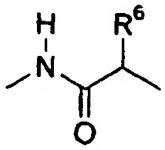


II

wherein S is a substrate,
L is a chemical bond or a linker,
A' is a chemical bond or a group of formula



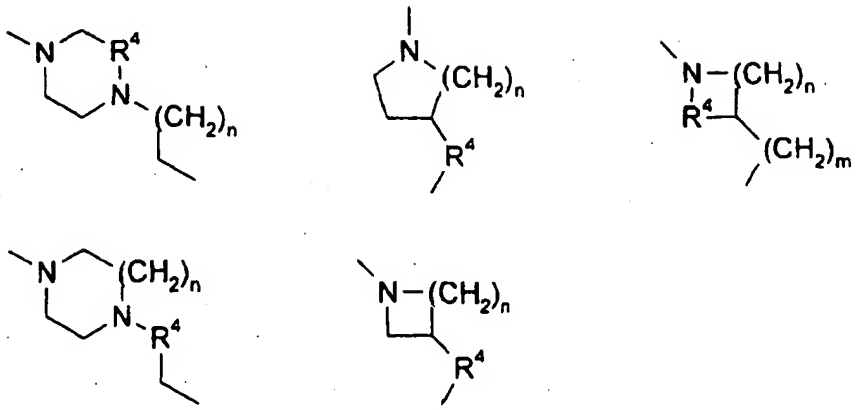
or



wherein R^4 is alkylene optionally substituted with hydrogen, alkyl, aryl, heteroaryl, alkoxy, aryloxy, cyano, hydroxy, dialkylamino, arylalkylamino, diarylamino or halogen;

R^5 is hydrogen, alkyl optionally substituted with hydroxy, halogen, cyano, alkoxy, aryloxy, dialkylamino, arylalkylamino or diarylamino; or aralkyl;

R^4 and R^5 may be covalently linked to each other by a covalent bond or an additional alkylene group R^4, preferentially giving rise to a fragment of the type shown below



wherein n and m are integers between 0 and 15, preferentially 0 and 3;

R^6 is hydrogen, alkyl, alkyl substituted with hydroxy, alkoxy, aryloxy, alkylthio, arylthio, dialkylamino, arylalkylamino or diarylamino; aralkyl, aryl, aryl substituted with alkyl, aryl, heteroaryl, halogen, alkoxy, aryloxy, dialkylamino, alkylarylamino, diarylamino, halogen, cyano, alkoxycarbonyl or aminocarbonyl;

R^1 is hydrogen, alkyl optionally substituted with hydroxy, halogen, cyano, alkoxy, aryloxy, dialkylamino, arylalkylamino or diarylamino; or aralkyl;

R^1 may be covalently linked to R^4, R^5 and/or R^6, in which case $-R^1-R^4-$ represents low alkylene, preferentially methylene, ethylene or propylene, unsubstituted or substituted with alkyl, hydroxy, alkoxycarbonyl, alkoxy or dialkylamino, $-R^1-R^5-$ represents ethylene or propylene, unsubstituted or substituted with alkyl, hydroxy, alkoxy or dialkylamino, and/or $-R^1-R^6-$ represents methylene, propylene or butylene unsubstituted or substituted with alkyl, hydroxy, alkoxycarbonyl, alkoxy or dialkylamino;

R^2 is alkyl optionally substituted with aryl, heteroaryl, alkoxy, aryloxy, cyano, hydroxy, dialkylamino, arylalkylamino, diarylamino, halogen or aminocarbonyl; aryl optionally substituted with alkyl, aryl, heteroaryl, halogen, alkoxy, aryloxy, dialkylamino, alkylarylamino, diarylamino, halogen, cyano, alkoxycarbonyl or aminocarbonyl; heteroaryl optionally substituted with alkyl, aryl, heteroaryl, halogen, alkoxy, aryloxy, dialkylamino, alkylarylamino, diarylamino, halogen, cyano, alkoxycarbonyl or aminocarbonyl; and

R^3 is alkyl optionally substituted with aryl, heteroaryl, alkoxy, aryloxy, cyano, hydroxy, dialkylamino, arylalkylamino, diarylamino or halogen: and

pharmaceutically acceptable salts thereof.

Presently in drug development, high throughput screening is playing a key role. High throughput screening generally incorporates automation and robotics, thus making it possible to screen thousands of compounds in one or more bioassays in a short period of time. This technique has created the need for an automated production of large numbers of different compounds for being screened. A robotic, fully automated system for the production and screening of highly diverse compounds as potential lead-candidates will dramatically speed up the discovery and optimization of new leads for all types of human diseases.

Traditionally, new compounds for lead-discovery or structural analogues for lead-optimization have been synthesized by multiple step linear syntheses. Linear syntheses involve the sequential reactions of several separate reactants in order to obtain the final product. Linear syntheses require the isolation, purification and characterization by spectroscopic and other analytical tools of the intermediate reaction products. Such a linear synthesis is therefore a very time consuming process, which requires a high skill in the synthetic organic chemical art. Since this traditional way of producing compounds is too inefficient for fully exploiting the screening-potential of presently available systems for high throughput screening, synthetic methodology is required, which permits the automated synthesis of large numbers of different compounds.

Parallel solid phase synthesis is today one of the fastest ways of producing arrays of single compounds or arrays of defined mixtures of compounds. However, there are still only few methods available for the parallel solid phase synthesis of organic compounds other than peptides or oligonucleotides. A principal disadvantage associated with peptidic or other bio-oligomeric leads is their low metabolic stability, due to *in vivo* proteolysis. For this reason, other type of compounds with a higher metabolic stability would be more attractive as leads. Of special interest in this context are small heterocyclic and heteroaromatic compounds, which have been proven to be very useful in many applications. Also as drugs for the treatment of different human metabolic disorders, small heterocyclic compounds have played and are playing a decisive role. For this reason, the solid phase synthesis of heterocyclic compounds is a highly demanded technology, which will be extremely valuable for the fast production of large numbers of potential leads for high volume throughput screening.

Triazoles are important core structures for biologically active compounds. They have been used in terms of nucleoside-analogues as antiviral agents and as purine nucleoside phosphorylase inhibitors (Comprehensive Medicinal Chemistry, Sammes, P. G. Ed.; Vol. 2, pp. 322, 460; Pergamon Press, 1990). Additionally, triazolodiazepines have been shown to be cholecystokinine antagonists (Bock, M. G. et al., *J. Med. Chem.* **1988**, *31*, 176) and platelet activating factor antagonists (Kornecki, E.; Ehrlich, Y. H.; Lenox, R. H. *Science (Washington D.C.)*, **1984**, *226*, 1454). Triazoles have also been used as adenosine antagonists (Trivedi, B. K.; Bruns, R. F. *J. Med. Chem.* **1988**, *31*, 1011), as anticonvulsants (references 20-22), as muscarinic agonists (reference 19), as antibiotics, such as cefatrizine, and may eventually be used as peptide mimics (Borg, S.; Estennebouhtou, G.; Luthman, K.; Csoregh, I.; Hesselink, W.; Hacksell, U. *J. Org. Chem.* **1995**, *60*, 3112-3120). The use of substituted 1,2,3-triazoles as peptide mimics has not yet been thoroughly investigated but it could dramatically increase the number of possible therapeutic applications of this class of compounds.

Many more 1,2,3-triazoles than those described so far may be postulated, however, to be potential drug candidates. To achieve the preparation and screening of a large number of compounds with triazole-core-structure, the present invention provides a solid phase synthesis for 1,2,3-triazoles in which variable substituent groups are independently attached to a common central triazole ring. The generally recognized advantages of solid phase synthesis are the absence of purification steps of intermediates or the final product, as well as the possibility of automation. Due to these features, a solid phase synthesis of 1,2,3-triazoles dramatically increases the synthesis efficiency for these therapeutically important compounds.

An overall illustration of the solid phase synthesis of 1,2,3-triazoles is shown in reaction Scheme I.

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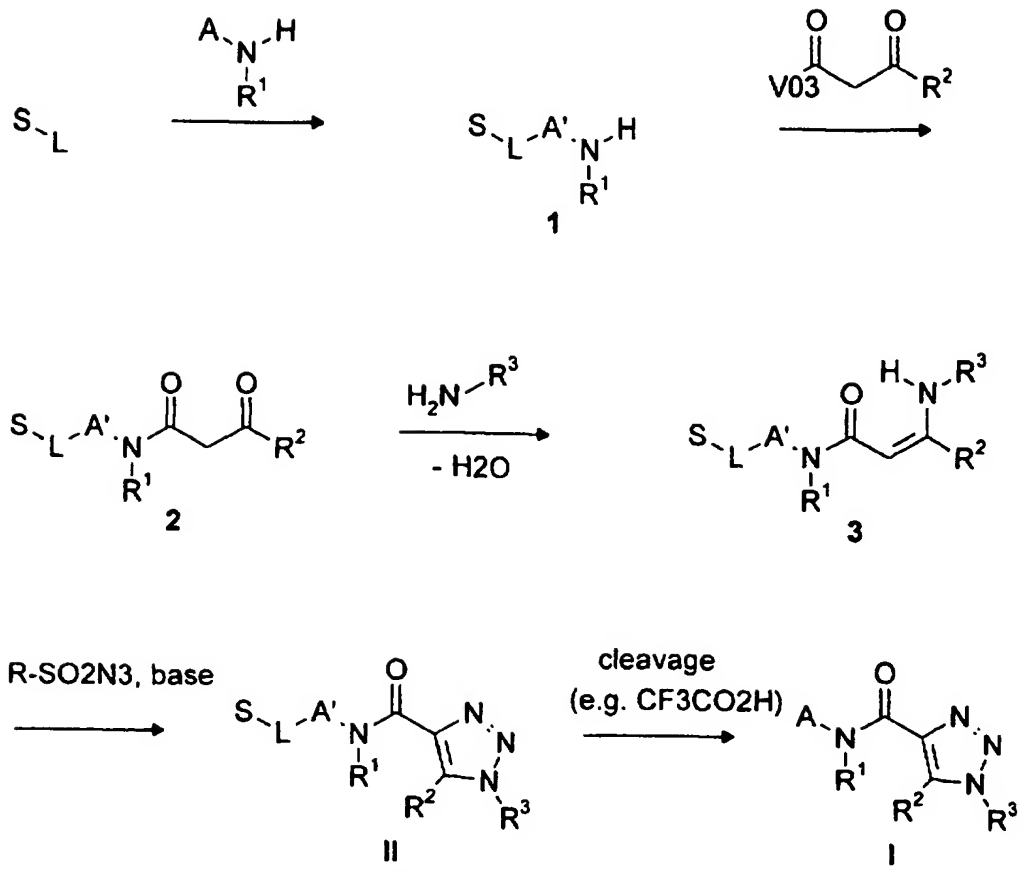
Scheme 1



In the following description of this invention, R is intended to be an organic radical. Alkyl is intended to mean lower straight, cyclic, fused or branched alkyl having 0 to 15 carbon atoms, preferentially 1 to 6 carbon atoms. Aryl is intended to mean phenyl or phenyl substituted with alkyl or phenyl, or phenyl fused with cycloalkyl, or polycyclic aromatic systems such as naphthyl, anthracenyl, phenanthrenyl, fluorenyl, etc. Alkylene is intended to mean lower straight, cyclic, fused or branched alkylene having 0 to 15 carbon atoms, preferentially 1 to 6 carbon atoms. Heteroaryl is intended to mean any of the possible isomeric, unsubstituted or alkyl-substituted pyrrolyl, furyl, thienyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, thiazolyl, oxadiazolyl, thiadiazolyl, pyridyl, pyrazinyl, pyrimidinyl and pyridazinyl, as well as the corresponding benzo and dibenzo derivatives or other fused ring-systems thereof. Heteroaryl is also intended to mean the partially or fully hydrogenated derivatives of the heterocyclic systems enumerated above. Alkoxy is intended to mean -O-alkyl and aryloxy is intended to mean -O-aryl. Cyano is intended to mean -CN, hydroxy is intended to mean -OH, amino is intended to mean $-NH_2$ and nitro is intended to mean $-NO_2$. Dialkylamino is intended to mean -

$N(alkyl)_2$. Alkylarylamino is intended to mean -N(alkyl)(aryl) and diarylamino is intended to mean $-N(aryl)_2$. Halogen is intended to mean -F, -Cl, -Br and -I. Aralkyl is intended to mean -alkylene-aryl. Alkylthio is intended to mean -S-alkyl and arylthio is intended to mean -S-aryl. Alkoxycarbonyl is intended to mean -CO-O-alkyl and aminocarbonyl is intended to mean $-CO-N(alkyl)_2$, -CO-N(alkyl)(aryl) or $-CO-N(aryl)_2$. Acylamino is intended to mean -N(alkyl)-CO-alkyl or -N(alkyl)-CO-aryl. A leaving group is intended to be a group or atom capable of existing in solution as a negatively charged species, or a positively charged group or atom.

In this synthesis, an organic molecule of the general formula $HN(R^5)-R^4-N(R^1)H$ or $HO_2C-CH(R^6)-N(R^1)P$, P being a protecting group, is attached to a substrate S via a linker L by well precedented methods, optionally followed by a deprotection step, in such a way, that a free primary or secondary amino group is generated on the substrate.

The substrate may be any insoluble or partially insoluble material, to which compounds may be covalently attached. Preferentially, the substrates may be selected from the group consisting of polystyrene, polyethylene glycol (PEG), polyethylene glycol attached to polystyrene (e.g. TentaGel), polyamides, polysaccharides and silicates. Depending on the type of substrate chosen, different types of solvents or protecting groups may be used.

Most preferentially, in the case of diamines attached to a substrate, a polystyrene resin or TentaGel resin, covalently attached to a Wang linker (Wang, S. *J. Am. Chem. Soc.* **1973**, *95*, 1328-1333), may first be treated with phosgene or a phosgene equivalent such as 4-nitrophenyl chloroformate or carbonyldiimidazole, in a suitable solvent such as DCM, THF, toluene, DMF or mixtures thereof, optionally in the presence of a base, such as pyridine, and then with an excess of a diamine, such as ethylenediamine, N,N'-dimethylethylenediamine, N,N'-diethylethylenediamine, N,N'-dipropylethylenediamine, N,N'-diisopropylethylenediamine, N,N'-dibutylethylenediamine, N,N'-dihexylethylenediamine, N,N'-dibenzylethylenediamine, N,N'-di(1-hydroxymethyl)propylethylenediamine, piperazine, 2-methylpiperazine, 2,6-dimethylpiperazine, 2,5-dimethylpiperazine, 1,4-diazacycloheptane, 6-hydroxy-1,4-diazacycloheptane, 6-acetoxy-1,4-diazacycloheptane, 1,2-diaminopropane, 1,3-diaminopropane, 1,3-diamino-2-propanol, N,N'-dimethyl-1,3-propanediamine, N,N'-diethyl-1,3-propanediamine, 2,2-dimethyl-1,3-propanediamine, N,N',2-trimethyl-1,3-propanediamine, 1,4-diaminobutane, N,N'-dipropyl-1,4-butane-

diamine, N,N'-diethylbutane-1,4-diamine, N,N'-dimethyl-2-butene-1,4-diamine, N,N'-diethyl-2-butene-1,4-diamine, N,N'-diethyl-2-butyne-1,4-diamine, 1,5-diaminopentane, 1,3-diaminopentane, 1,2-diaminocyclohexane, 1,3-diaminocyclohexane, 1,4-diaminocyclohexane, 1,3-bis(aminomethyl)cyclohexane, 1,4-bis(aminomethyl)-cyclohexane, 4,4'-bipiperidine, 1-[2-(3-pyridylmethylamino)ethyl]-piperazine, 1-(2-aminoethyl)piperazine, 4-aminomethylpiperidine, 3-(4-aminobutyl)piperidine, 5-amino-2,2,4-trimethyl-1-cyclopentanemethylamine, 4,4'-diaminodicyclohexylmethane, o-xylylenediamine, m-xylylenediamine, p-xylylenediamine or isophoronediamine, to give a substrate-bound diamine of the general formula [polystyrene]-[Wang linker]-O-CO-N(R^5)-R^4-N(R^1)H. The preparation of such substrate-bound diamines has occasionally been described in literature (e.g. Hiroshige, M.; Hauske, J. R.; Zhou, P. *J. Am. Chem. Soc.* **1995**, *117*, 11590-11591; Zaragoza, F. *Tetrahedron Lett.* **1995**, *36*, 8677-8678; Dixit, D. M.; Leznoff, C. C. *Israel J. Chem.* **1978**, *17*, 248-252; Dixit, D. M.; Leznoff, C. C. *J. Chem . Soc. , Chem. Commun.* **1977**, 798-799; Kaljuste, K.; Unden, A. *Tetrahedron Lett.* **1995**, *36*, 9211-9214).

In the case of protected amino acids attached to a substrate, a polystyrene resin or TentaGel, covalently attached to a Rink linker (H. Rink, *Tetrahedron Lett.* **1987**, *28*, 3787), may be acylated with a derivative of a side-chain and nitrogen-protected (e.g. FMoc) amino acid, such as FMoc-glycine, FMoc-phenylglycine, FMoc-sarcosine, FMoc-alanine, FMoc-valine, FMoc-norvaline, FMoc-leucine, FMoc-isoleucine, FMoc-norleucine, FMoc-penicillamine, FMoc-arginine, FMoc-asparagine, FMoc-aspartic acid, FMoc-citrulline, FMoc-glutamine, FMoc-glutamic acid, FMoc-proline, FMoc-hydroxyproline, FMoc-phenylalanine, FMoc-tyrosine, FMoc-tryptophan, FMoc-threonine, FMoc-histidine, FMoc-serine, FMoc-cysteine, FMoc-methionine, FMoc-lysine, FMoc-statine or FMoc-ornithine, by well established procedures, for example with the *in situ* generated symmetric anhydride of these amino acid derivatives. Most of the FMoc-amino acids and some of the resulting substrate-bound FMoc-amino acids are commercially available. After this acylation step, the nitrogen protecting group may be removed by well established methods, such as treatment with piperidine in DMF in the case of an FMoc-protecting group, to give a substrate-bound amino acid of the general formula [polystyrene or Tentagel]-[Rink linker]-NH-CO-C(R^6)H-N(R^1)H. Also non-natural amino acid derivatives may be attached to a substrate-bound Rink linker and converted, by an optional deprotection step, into support-bound amino acids of the type **1** (scheme 1).

The substrate bound primary or secondary amine **1** may then be acylated with an appropriate 3-oxoalkanoic acid derivative of the general formula R^2-CO-CH_2-CO-X, X being a leaving group, preferentially with the phenyl ester (X = OPh) or 4-nitrophenyl ester, in an appropriate solvent such as DMF, DCM, THF, toluene or mixtures thereof. Alternatively, other, *in situ* generated or isolated derivatives of 3-oxoalkanoic acids may be used as acylating reagents, such as the symmetric anhydride or mixed anhydrides derived from alkyl chloroformates and the corresponding 3-oxoalkanoic acid, or the imidazolide or other types of activated esters, obvious to those skilled in the art.

Other than commercially available 3-oxoalkanoic acids may be used in this synthetic sequence, since numerous 3-oxoalkanoic acids can easily be prepared, for instance from ketones (e.g. Bottaccio, G.; Chiusoli, G. P. *Chem. Commun.* **1966**, 618; Pelletier, S. W.; Chappell, R. L.; Parthasarathy, P. C.; Lewin, N. *J. Org. Chem.* **1966**, *31*, 1747-1752; Corey, E. J.; Chen, R. K. H. *J. Org. Chem.* **1973**, *38*, 4086; Jp. Pat. 8 203 663 (1982), Mitsui Toatse Chemicals, Chem. Abstr. **1982**, *96*, 199 101).

Alternatively, a 3-oxoalkanoic acid derivative may be directly reacted with a Ring linker attached to a substrate, to give a derivative of the general formula [substrate]-[Rink linker]-NH-CO-CH_2-CO-R^2. This corresponds to the case, where A' (scheme 1) is a chemical bond and A is hydrogen.

The group R^2 may be straight or branched alkyl groups, such as methyl, ethyl, propyl, isopropyl, butyl, including n-butyl, sec-butyl, iso-butyl, tert-butyl, pentyl, hexyl, heptyl, octyl, etc., and their variants, straight or branched alkylene chains such as methylene, 1,2-ethylene, 1,1-ethylene, propylene, etc. linked to hydrogen, cycloalkyl groups, substituted or unsubstituted aryl groups such as phenyl, naphthyl, biphenylyl or monovalent radicals of substituted or unsubstituted heterocycles and heteroaromatics such as pyridyl, thienyl, pyrrolyl, furyl, piperidinyl, pyrrolidinyl, etc. Additionally, R^2 may be substituted or unsubstituted aryl groups or substituted or unsubstituted heterocycles or heteroaromatics. All these groups may also be substituted with functional groups such as F, Cl, Br, I, $CONR_2$, CO_2R, CN, NO_2, SR, SOR, SO_2R, SO_2NR_2, OR or NR_2, R being hydrogen, low alkyl or aryl.

The resulting, substrate-bound 3-oxoamide **2** may then be treated with an excess of a primary amine of the general formula R^3-NH_2 in the presence of a water-removing agent, preferentially a trialkyl orthoformate, to yield an enamine **3**.

Preferred primary amines of the general formula R^3-NH_2 are amines, where R^3 is straight or branched alkyl groups, such as methyl, ethyl, propyl, isopropyl, butyl, including n-butyl, sec-butyl, iso-butyl, tert-butyl, pentyl, hexyl, heptyl, octyl, etc., and their variants, straight or branched alkylene chains such as methylene, 1,2-ethylene, 1,1-ethylene, propylene, etc. linked to hydrogen, cycloalkyl groups, substituted or unsubstituted aryl groups such as phenyl, naphthyl, biphenylyl or monovalent radicals of substituted or unsubstituted heterocycles and heteroaromatics such as pyridyl, thienyl, pyrrolyl, furyl, piperidinyl, pyrrolidinyl, etc. All these groups may also be substituted with functional groups such as -F, -Cl, -Br, -I, -N(R)CONR$_2$, -N(R)CO$_2$R, -CONR$_2$, -CO$_2$R, -CN, -NO$_2$, -SR, -SOR, -SO$_2$R, -SO$_2$NR$_2$, -OR or -NR$_2$, R being hydrogen, low alkyl or aryl.

In some cases, the enamine-formation also occurs in the absence of a dehydrating agent, especially if DMF is chosen as solvent. The most appropriate solvent will depend on the type of substrate chosen. For the case of polystyrene, a mixture of DMF with the trialkyl orthoformate, preferentially triethyl orthoformate or trimethyl orthoformate may be an appropriate solvent/dehydratant system.

The resulting enamine **3** may then be treated with a sulfonyl azide and a base, preferentially *p*-toluenesulfonyl azide, methanesulfonyl azide or 4-acetamido benzenesulfonyl azide in the presence of a tertiary amine, preferentially diisopropylethylamine, thereby inducing cyclization to the triazole **4**. The most appropriate solvent will depend on the type of substrate chosen. This reaction may be carried out in acetonitrile, DMF or protic solvents, but if the substrate is a polystyrene-based resin, then DMF may be an appropriate solvent.

Cleaving of the linker of the product **4** may release the triazole derivative **5** into solution. Cleavage conditions will depend upon the type of substrate and linker chosen. E. g., in the case of a polystyrene resin with a Wang linker or a Rink amide linker, treatment of the support-bound triazole **4** with TFA may lead to a cleavage of the linker. These strongly acidic reaction conditions do not lead to a destruction of the 1,2,3-triazoles of the general formula I.

Using this synthetic method, arrays of triazole derivatives may be constructed with the help of a device for parallel solid phase synthesis. This may be either the pin method developed by Geysen et al. (*J. Immunol. Meth.* **1987**, *102*, 259-274) or a device with several reactors for solid phase synthesis (containers with a permeable wall), which permits the automated addition of reagents and solvents, as well as the removal of the solvents from the reactors by simultaneous or individual application of a pressure difference between the inside and the outside of the permeable wall of the reactors.

Such an array may be prepared on a multiple organic synthesizer (e.g. "ACT 496" of "Advanced ChemTech") by reacting under the conditions specified below different amines attached to a substrate and located in individual containers with different 3-oxoalkanoic acid derivatives. The resulting intermediates **2** may then be reacted with different primary amines in the presence of a water-removing agent and then with a sulfonyl azide in the presence of a base to give, after optional cleavage from the substrate, an array of different triazole derivatives.

The present invention also permits the synthesis of arrays of mixtures of 1,2,3-triazole derivatives. This can be achieved either by the "split and mix" method (Sepetov, N.F., Krchnák, V., Stankova, M., Wade, S., Lam, K.S., and Lebl *Proc. Natl. Acad. Sci. USA* **1995**, *92*, 5426-5430) or by using mixtures of the corresponding reagents.

By virtue of the present invention basically two different types of arrays of triazoles I or II may be constructed: fully combinatorial arrays (FCA) and not-fully combinatorial arrays (NFCA).

By FCA we refer to arrays of substituted triazoles, in which all the possible combinations of a set of selected building blocks (R-groups) are realized. As an example, a FCA of *N* triazoles may be prepared by selecting *n* diamines, *m* 3-oxoalkanoic acids and *p* primary amines so that $n \times m \times p = N$, and synthesizing all the *N* possible combinations of diamine/3-oxoalkanoic acid/primary amine. The selection of building blocks may be done with regard to the expected properties of the members of the array.

By NFCA we refer to arrays of substituted triazoles, in which only a selection of the possible combinations of a set of selected building blocks is realized. As an

example, a NFCA of *N* triazoles may be prepared by first selecting *n* diamines, *m* 3-oxoalkanoic acids and *p* primary amines so that $n \times m \times p > N$. Then a selection of *N* triazoles from all the $n \times m \times p$ theoretically possible triazoles is done by grouping all the $n \times m \times p$ possible triazoles into *N* groups of triazoles with similar expected properties and selecting from each of these groups one triazole, which is then synthesized. The selection of building blocks and of triazoles may be done with regard to the expected properties of the members of the array.

For the preparation of such arrays of compounds, the exact positions of the substrate does, by itself, not give any structural information about the compound prepared on this particular batch of substrate. For this reason, the spatial arrangement of the substrate is irrelevant. Structural information will be accessible only from the records of the sequences of reagents added to each batch of substrate. In every step of the preparation of a FCA or a NFCA, the exact location of one substrate-container within the array of containers and the structure of the different reagents added to this container is recorded, so that the precise structure of the triazole resulting from one given container can always be deduced.

The resulting arrays of 1,2,3-triazoles may then be screened by comparing the individual triazoles in terms of their ability to bind to a particular receptor or to induce a particular biological process or to catalyze a biological or chemical reaction. This can be achieved basically in two different ways. One possibility may be the screening of the substrate-bound triazoles **II**, e.g. against a soluble receptor. This could for instance be a radioactively labelled peptide or enzyme, which would easily permit to determine the binding of a given triazole **II** to this peptide by washing away the excess of radioligand used and determining the remaining radioactivity of each substrate-bound triazole **II**-peptide complex. Alternatively, as a further example, catalytic activity of the different substrate-bound triazoles **II** for a given biological process or a chemical reaction may be measured by comparing the speed at which this biological process or a chemical reaction takes place in the presence and in the absence of a given substrate-bound triazole **II**.

The second option for screening may consist in screening the triazoles **I**, after having cleaved the linker of the substrate-bound triazoles **II** and using appropriately charged and indexed Microtiter plates of similar multiwell arrangements, in solution against a substrate-bound receptor or enzyme. The screening of soluble small molecules is conventional and well known. Typically, radioassays are being used, in

which the competitive binding of the radiolabelled, natural ligand of a given receptor and the compound to be tested for binding to this receptor is investigated.

An example would be a screening against the cholecystokinine receptors, which are widely distributed throughout the central and peripheral nervous system and mediate numerous physiological responses. Crude membrane homogenates may be prepared according to the procedure described by Chang et al. (Proc. Natl. Acad. Sci. **1986**, 4923-4926) and radiolabelled cholecystokinine can be purchased from New England Nuclear, Massachusetts, U.S.A. Other examples will be readily apparent to those skilled in the arts of physiology, biology and biotechnology. These could for instance be the somatostatine receptors, the glucagon receptors, the insulin receptor, etc.

Alternatively, functional or other assays may be used, in which for example the biological response of a cell or a genetically modified or unmodified organism is measured as a function of the amount of test-substance added to this organism. As a further example, the catalytic activity of the different triazoles I for a given biological process or a chemical reaction may be measured by comparing the speed at which this biological process or a chemical reaction takes place in the presence and in the absence of a given triazole I.

The methods described above may be used to prepare and screen large numbers of compounds in a reasonable amount of time. Synthesis may be combined with screening in various different ways to screen compounds in unusually large arrays.

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Examples

Preparation of resin-bound 3-oxobutyrylpiperazine

To a suspension of Wang resin (45.0 g, 42.3 mmol, Novabiochem, loading: 0.94 mmol/g) in dichloromethane (DCM, 600 mL) first pyridine (52 mL) and then a solution of 4-nitrophenyl chloroformate (43.0 g, 231 mmol) were added. After shaking for 3 h at room temperature the mixture was filtered, the resin was washed with DCM (5 x 300 mL) and then added to a cold solution of piperazine (38.2 g, 444 mmol) in DMF (600 mL). The resulting mixture was stirred for 13 h, filtered and the resin was washed extensively with DMF, DCM and methanol. After drying, approx. 45 g of resin-bound piperazine was obtained.

To a suspension of this resin (0.60 g, approx. 0.6 mmol) in DMF (4 mL) a freshly prepared solution of 3-oxobutyric acid phenyl ester (5 equivalents, prepared by refluxing a solution of phenol and 2,2,6-trimethyl-1,3-dioxin-4-one in toluene for 1 h

and used without isolation; preparation described by Clemens, R. J.; Hyatt, J. A. *J. Org. Chem.* **1985**, *50*, 2431-2435) in toluene (6 mL) was added, followed by the addition of diisopropylethylamine (2 mL). The resulting mixture was shaken for 2 h, filtered, the resin was washed with DMF and the acylation was then repeated once as described above for 3 h. Washing with DMF yielded resin-bound 3-oxobutyrylpiperazine, which was used for the following reactions without drying.

General procedure for the solid phase synthesis of 1,2,3-triazole-4-carboxylic acid amides

To the resin-bound 3-oxobutyramide (prepared as described above from 0.60 g of resin-bound piperazine; approx. 0.6 mmol) a solution of the primary amine (3.0 mmol) in DMF (4 mL) was added, followed by the addition of triethyl orthoformate (4 mL). The resulting mixture was shaken for 24 h and then filtered. The resin was washed with DMF (2 x 10 mL) and then a solution of *p*-toluenesulfonyl azide (0.60 mL, 3.84 mmol) in DMF (6 mL) was added to the resin, followed by the addition of diisopropylethylamine (2 mL). After shaking for 24 h the mixture was filtered and carefully washed with DMF, methanol, DCM and 10% AcOH in DCM. It was then suspended in a solution of 60% TFA in DCM (8 mL) and shaken for 3 h. Filtration, washing with DCM and concentration of the combined filtrates gave the crude triazoles as oils.

[5-Methyl-4-(piperazine-1-carbonyl)-1H-1,2,3-triazol-1-yl]acetic acid benzyl ester trifluoroacetate

HPLC (Lichrosorb RP 18, acetonitrile/water gradient, monitoring at 254 nm): elution at 13.3 min, 65% pure. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.34 (s, 3H), 3.20 (m, 4H), 3.82 (m, 2H), 4.18 (m, 2H), 5.21 (s, 2H), 5.57 (s, 2H), 7.39 (s, br, 5H), 8.99 (s, br, 2H). For analytical purposes, this compound was derivatized by conversion into the corresponding 2-tolylurea by reaction with 2-methylphenyl isocyanate. The triazole obtained from 0.60 g of starting Wang resin gave 201 mg (70%) of the 2-tolylurea. Colourless solid, m.p. 125-127°C (ethyl acetate). Anal. Calcd. for $C_{25}H_{28}N_6O_4$ (476.53): C, 63.01; H, 5.92; N, 17.64. Found: C, 62.93; H, 6.06; N, 17.10.

[1-(4-Methoxybenzyl)-5-methyl-1H-1,2,3-triazol-1-yl]piperazin-1-ylmethanone trifluoroacetate

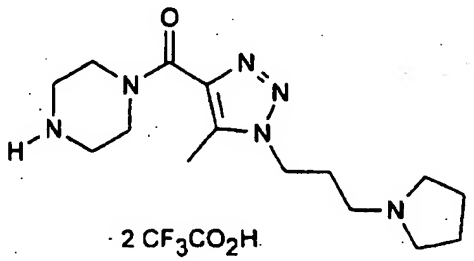
HPLC (Lichrosorb RP 18, acetonitrile/water gradient, monitoring at 254 nm): elution at 10.3 min, 52% pure. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.37 (s, 3H), 3.20 (m, 4H), 3.72 (s, 3H), 3.80 (m, 2H), 4.17 (m, 2H), 5.55 (s, 2H), 6.92 (d, J = 8.0 Hz, 2H), 7.19 (d, J = 8.0 Hz, 2H), 8.93 (s, br, 2H). For analytical purposes, this compound was derivatized by conversion into the corresponding 4-chlorophenylurea by reaction with 4-chlorophenyl isocyanate. The triazole obtained from 1.20 g of starting Wang resin gave 190 mg (34%) of the 4-chlorophenylurea. Colourless solid, m.p. 202-204°C (ethyl acetate). Anal. Calcd. for $C_{23}H_{25}ClN_6O_3$ (468.94): C, 58.91; H, 5.37; N, 17.92. Found: C, 59.03; H, 5.45; N, 17.72.

{1-[2-(4-Nitrophenyl)ethyl]-5-methyl-1H-1,2,3-triazol-1-yl}piperazin-1-ylmethanone trifluoroacetate

Yield of crude trifluoroacetate: 75%. HPLC (Lichrosorb RP 18, acetonitrile/water gradient, monitoring at 254 nm): elution at 14.6 min, 82% pure. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.37 (s, 3H), 3.15 (m, 4H), 3.30 (t, J = 7.0 Hz, 2H), 3.82 (m, 2H), 4.15 (m, 2H), 4.64 (t, J = 7.0 Hz, 2H), 7.45 (d, J = 8.0 Hz, 2H), 8.13 (d, J = 8.0 Hz, 2H), 9.01 (s, br, 2H). For analytical purposes, this compound was derivatized by conversion into the corresponding acetamide by reaction with acetic anhydride. The resulting product was identical to the compound obtained from 1-acetylpiperazine by acetoacetylation (Clemens, R. J.; Hyatt, J. A. *J. Org. Chem.* **1985**, *50*, 2431-2435), condensation with 4-nitrophenylethylamine and cyclization by treatment with *p*-toluenesulfonyl azide and triethylamine. Colourless solid, m.p. 142-144 °C (ethyl acetate). Anal. Calcd. for $C_{18}H_{22}N_6O_4$ (386.41): C, 55.95; H, 5.74; N, 21.74. Found: C, 56.13; H, 5.93; N, 21.28.

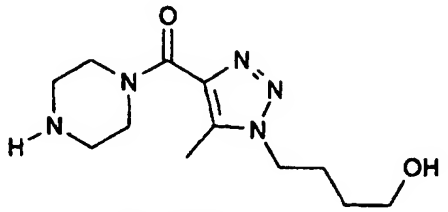
Following this procedure, the following triazole derivatives have been prepared:

[5-methyl-1-(3-pyrrolidin-1-ylpropyl)-1H-1,2,3-triazol-4-yl]piperazin-1-yl-methanone trifluoroacetate



^{1}H NMR (400 MHz, DMSO-d_6) δ 1.86 (m, 2H), 2.00 (m, 2H), 2.21 (m, 2H), 2.30 (s, 3H), 2.99 (m, 2H), 3.18 (m, 6H), 3.57 (m, 2H), 3.81 (m, 4H), 4.15 (m, 2H), 8.92 (s, br, 3H).

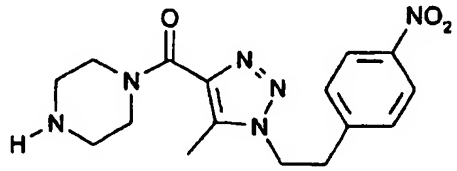
[1-(4-hydroxybutyl)-5-methyl-1H-1,2,3-triazol-4-yl]piperazin-1-yl-methanone trifluoroacetate



· CF_3CO_2H

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.71 (m, 2H), 1.89 (m, 2H), 2.45 (s, 3H), 3.19 (m, 4H), 3.81 (m, 2H), 4.17 (m, 2H), 4.30-4.43 (m, 4H), 8.98 (m, 2H).

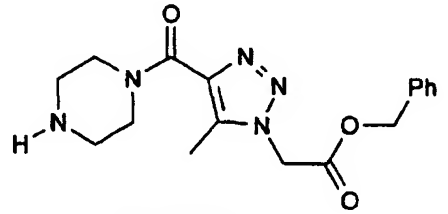
{1-[2-(4-nitrophenyl)ethyl]-5-methyl-1H-1,2,3-triazol-4-yl}piperazin-1-yl-methanone trifluoroacetate



· CF_3CO_2H

HPLC (Lichrosorb RP 18, acetonitrile/water gradient, monitoring at 254 nm): elution at 14.6 min, 82% pure. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.37 (s, 3H), 3.15 (m, 4H), 3.30 (t, J = 7.0 Hz, 2H), 3.82 (m, 2H), 4.15 (m, 2H), 4.64 (t, J = 7.0 Hz, 2H), 7.45 (d, J = 8.0 Hz, 2H), 8.13 (d, J = 8.0 Hz, 2H), 9.01 (s, br, 2H).

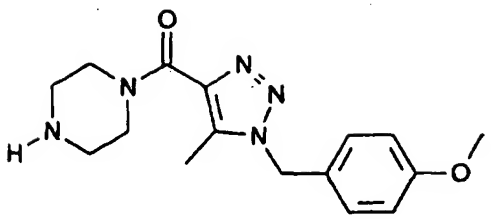
[5-methyl-4-(piperazin-1-carbonyl)-1H-1,2,3-triazol-1-yl]acetic acid benzyl ester trifluoroacetate



· CF_3CO_2H

HPLC (Lichrosorb RP 18, acetonitrile/water gradient, monitoring at 254 nm): elution at 13.3 min, 65% pure. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.34 (s, 3H), 3.20 (m, 4H), 3.82 (m, 2H), 4.18 (m, 2H), 5.21 (s, 2H), 5.57 (s, 2H), 7.39 (s, br, 5H), 8.99 (s, br, 2H).

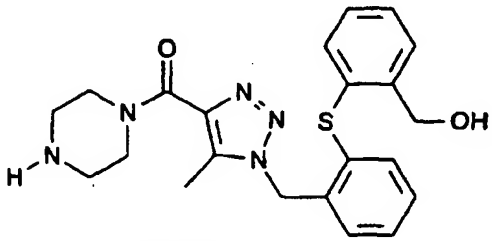
[1-(4-methoxybenzyl)-5-methyl-1H-1,2,3-triazol-4-yl]piperazin-1-yl-methanone trifluoroacetate



$\cdot CF_3CO_2H$

HPLC (Lichrosorb RP 18, acetonitrile/water gradient, monitoring at 254 nm): elution at 10.3 min, 52% pure. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.37 (s, 3H), 3.20 (m, 4H), 3.72 (s, 3H), 3.80 (m, 2H), 4.17 (m, 2H), 5.55 (s, 2H), 6.92 (d, J = 8.0 Hz, 2H), 7.19 (d, J = 8.0 Hz, 2H), 8.93 (s, br, 2H).

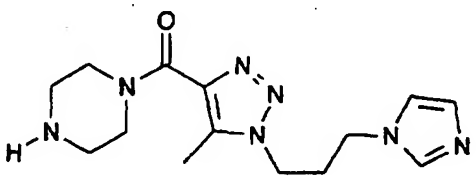
{1-[2-(2-hydroxymethyl)phenylthio]benzyl-5-methyl-1H-1,2,3-triazol-4-yl)piperazin-1-ylmethanone trifluoroacetate



$\cdot CF_3CO_2H$

HPLC (Lichrosorb RP 18, acetonitrile/water gradient, monitoring at 254 nm): elution at 15.0 min, 72% pure. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.33 (s, 3H), 3.15 (m, 4H), 3.79 (m, 2H), 4.14 (m, 2H), 4.54 (s, 2H), 5.63 (s, 2H), 6.90-7.20 (m, 8H), 8.99 (m, 2H).

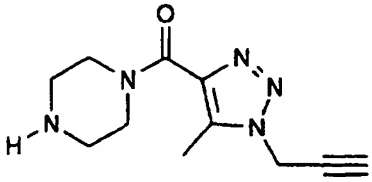
[5-methyl-1-(3-imidazol-1-ylpropyl)-1H-1,2,3-triazol-4-yl]piperazin-1-yl-methanone trifluoroacetate



$\cdot 2\ CF_3CO_2H$

^{1}H NMR (400 MHz, DMSO-d_6) δ 2.35-2.49 (m, 5H), 3.18 (m, 4H), 3.82 (m, 2H), 4.15 (m, 2H), 4.29 (t, J = 7.5 Hz, 2H), 4.40 (t, J = 7.5 Hz, 2H), 7.71 (s, 1H), 7.80 (s, 1H), 9.05 (m, 4H).

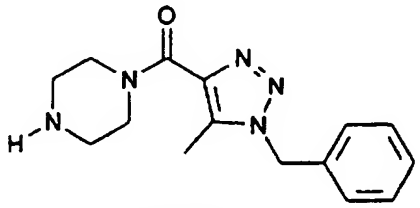
[5-methyl-1-(propin-3-yl)-1H-1,2,3-triazol-4-yl]piperazin-1-yl-methanone trifluoroacetate



· CF_3CO_2H

^{1}H NMR (400 MHz, DMSO-d_6) δ 2.37 (s, 3H), 3.18 (m, 4H), 3.61 (t, J = 3.2 Hz, 1H), 3.79 (m, 2H), 4.13 (m, 2H), 5.38 (d, J = 3.2 Hz, 2H), 9.02 (m, 2H).

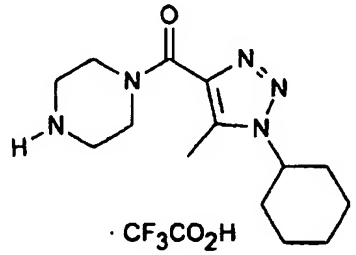
(5-methyl-1-benzyl-1H-1,2,3-triazol-4-yl)piperazin-1-yl-methanone trifluoroacetate



· CF_3CO_2H

^{1}H NMR (400 MHz, DMSO-d_6) δ 2.37 (s, 3H), 3.13 (m, 4H), 3.81 (m, 2H), 4.18 (m, 2H), 5.67 (s, 2H), 7.20-7.50 (m, 5H), 9.05 (s, 2H).

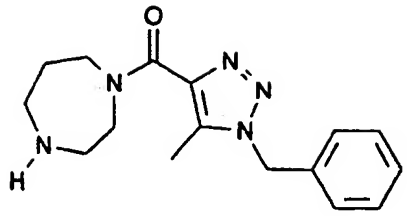
(1-cyclohexyl-5-methyl-1H-1,2,3-triazol-4-yl)piperazin-1-yl-methanone trifluoroacetate



· CF_3CO_2H

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.40-2.01 (m, 10H), 2.46 (s, 3H), 3.22 (m, 4H), 3.81 (m, 2H), 4.14 (m, 2H), 4.34 (m, 1H), 9.02 (m, 2H).

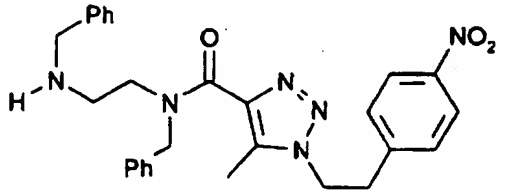
(1-benzyl-5-methyl-1H-1,2,3-triazol-4-yl)-1,4-diazepan-1-yl-methanone trifluoroacetate



$\cdot CF_3CO_2H$

^1H NMR (400 MHz, DMSO-d_6) δ 1.95-2.12 (m, 2H), 2.37 (m, 3H), 3.18-3.32 (m, 4H), 3.42 (m, 1H), 3.66 (m, 1H), 3.81 (m, 1H), 4.04 (m, 1H), 5.64 (s, 2H), 7.20-7.40 (m, 5H), 8.85 (m, 2H).

1-[2-(4-nitrophenyl)ethyl]-5-methyl-1H-1,2,3-triazole-4-carboxylic acid benzyl-(2-benzylamino)ethylamide trifluoroacetate



$\cdot CF_3CO_2H$

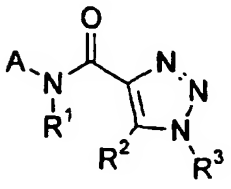
HPLC (Lichrosorb RP 18, acetonitrile/water gradient, monitoring at 254 nm): elution at 16.9 min, 41% pure. ^1H NMR (complexity due to the presence of two amide-bond rotamers, 400 MHz, DMSO-d_6) δ 2.30 (s, 1.5H), 2.42 (s, br, 1.5H), 3.18 (m, 2H), 3.28-3.40 (m, 2H), 4.20 (m, 4H), 4.68 (m, 1H), 5.10 (m, 1H), 7.20-7.52 (m, 12H), 8.13 (d, J = 8.0 Hz, 2H), 8.96 (s, br, 2H).

Conclusion

The above description is illustrative and not restrictive. Various modifications and variations of the invention will become apparent to those of skill in the art upon review of this disclosure. Merely by way of example a wide variety of process times, reaction temperature as well as different ordering of certain processing steps may be utilized. The scope of the invention should, therefore, be determined, not with reference to the above description, but instead should be determined with reference to the appended claims along with their full scope of equivalents.

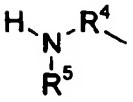
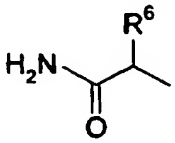
Claims

1. A compound of the general formula I



I

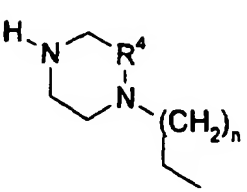
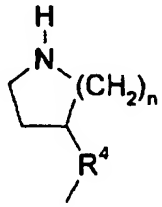
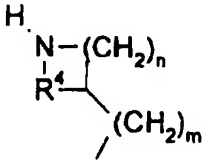
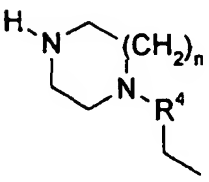
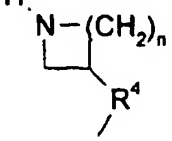
wherein A is a hydrogen atom or a group of formula

 or 

wherein R^4 is alkylene optionally substituted with hydrogen, alkyl, aryl, heteroaryl, alkoxy, aryloxy, cyano, hydroxy, dialkylamino, arylalkylamino, diarylamino or halogen;

R^5 is hydrogen, alkyl optionally substituted with hydroxy, halogen, cyano, alkoxy, aryloxy, dialkylamino, arylalkylamino or diarylamino; or aralkyl;

R^4 and R^5 may be covalently linked to each other by a covalent bond or an additional alkylene group R^4, preferentially giving rise to a fragment of the type shown below

wherein n and m are integers between 0 and 15;

R^6 is hydrogen, alkyl, alkyl substituted with hydroxy, alkoxy, aryloxy, alkylthio, arylthio, dialkylamino, arylalkylamino or diarylamino; aralkyl, aryl, aryl substituted with alkyl, aryl, heteroaryl, halogen, alkoxy, aryloxy, dialkylamino, alkylarylamino, diarylamino, halogen, cyano, alkoxycarbonyl or aminocarbonyl;

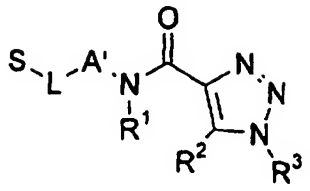
R^1 is hydrogen, alkyl optionally substituted with hydroxy, halogen, cyano, alkoxy, aryloxy, dialkylamino, arylalkylamino or diarylamino; or aralkyl;

R^1 may be covalently linked to R^4, R^5 and/or R^6, in which case $-R^1-R^4-$ represents low alkylene, unsubstituted or substituted with alkyl, hydroxy, alkoxycarbonyl, alkoxy or dialkylamino, $-R^1-R^5-$ represents ethylene or propylene, unsubstituted or substituted with alkyl, hydroxy, alkoxy or dialkylamino, and/or $-R^1-R^6-$ represents methylene, propylene or butylene unsubstituted or substituted with alkyl, hydroxy, alkoxycarbonyl, alkoxy or dialkylamino;

R^2 is alkyl optionally substituted with aryl, heteroaryl, alkoxy, aryloxy, cyano, hydroxy, dialkylamino, arylalkylamino, diarylamino, halogen or aminocarbonyl;
aryl optionally substituted with alkyl, aryl, heteroaryl, halogen, alkoxy, aryloxy, dialkylamino, alkylarylamino, diarylamino, halogen, cyano, alkoxycarbonyl or aminocarbonyl;
heteroaryl optionally substituted with alkyl, aryl, heteroaryl, halogen, alkoxy, aryloxy, dialkylamino, alkylarylamino, diarylamino, halogen, cyano, alkoxycarbonyl or aminocarbonyl; and

R^3 is alkyl optionally substituted with aryl, heteroaryl, alkoxy, aryloxy, cyano, hydroxy, amino, dialkylamino, arylalkylamino, diarylamino or halogen; and pharmaceutically acceptable salts thereof.

2. A compound of the general formula II

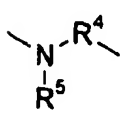
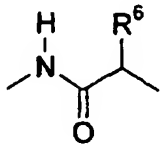


II

wherein S is a substrate,

L is a chemical bond or a linker,

A' is a chemical bond or a group of formula

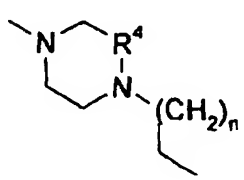
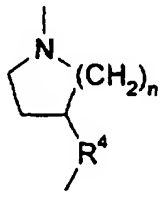
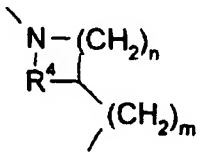
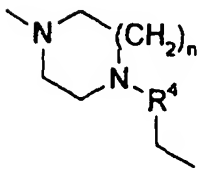
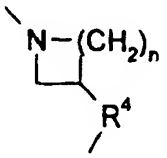
 or 

wherein

R^4 is alkylene optionally substituted with hydrogen, alkyl, aryl, heteroaryl, alkoxy, aryloxy, cyano, hydroxy, dialkylamino, arylalkylamino, diarylamino or halogen;

R^5 is hydrogen, alkyl optionally substituted with hydroxy, halogen, cyano, alkoxy, aryloxy, dialkylamino, arylalkylamino or diarylamino; or aralkyl;

R^4 and R^5 may be covalently linked to each other by a covalent bond or an additional alkylene group R^4, preferentially giving rise to a fragment of the type shown below

wherein n and m are integers between 0 and 15;

R^6 is hydrogen, alkyl, alkyl substituted with hydroxy, alkoxy, aryloxy, alkylthio, arylthio, dialkylamino, arylalkylamino or diarylamino; aralkyl, aryl, aryl substituted with alkyl, aryl, heteroaryl, halogen, alkoxy, aryloxy, dialkylamino, alkylarylamino, diarylamino, halogen, cyano, alkoxycarbonyl or aminocarbonyl;

R^1 is hydrogen, alkyl optionally substituted with hydroxy, halogen, cyano, alkoxy, aryloxy, dialkylamino, arylalkylamino or diarylamino; or aralkyl;

R^1 may be covalently linked to R^4, R^5 and/or R^6, in which case $-R^1-R^4-$ represents low alkylene, unsubstituted or substituted with alkyl, hydroxy, alkoxycarbonyl, alkoxy or dialkylamino, $-R^1-R^5-$ represents ethylene or propylene, unsubstituted or substituted with alkyl, hydroxy, alkoxy or dialkylamino, and/or $-R^1-R^6-$ represents methylene, propylene or butylene unsubstituted or substituted with alkyl, hydroxy, alkoxycarbonyl, alkoxy or dialkylamino;

R^2 is alkyl optionally substituted with aryl, heteroaryl, alkoxy, aryloxy, cyano, hydroxy, dialkylamino, arylalkylamino, diarylamino, halogen or aminocarbonyl;
aryl optionally substituted with alkyl, aryl, heteroaryl, halogen, alkoxy, aryloxy, dialkylamino, alkylarylamino, diarylamino, halogen, cyano, alkoxycarbonyl or aminocarbonyl;
heteroaryl optionally substituted with alkyl, aryl, heteroaryl, halogen, alkoxy, aryloxy, dialkylamino, alkylarylamino, diarylamino, halogen, cyano, alkoxycarbonyl or aminocarbonyl; and

R^3 is alkyl optionally substituted with aryl, heteroaryl, alkoxy, aryloxy, cyano, hydroxy, dialkylamino, arylalkylamino, diarylamino or halogen; and

pharmaceutically acceptable salts thereof.

3. A method for preparing a compound according to claim 1 comprising the steps of:

a) acylation of a substrate-bound free primary or secondary amine of the formula S-L-A'-N(R^1)H, wherein S, L, A' and R^1 are as defined in claim 2, with a 3-oxoalkanoic acid derivative of the general structure R^2-CO-CH_2-COX, wherein R^2 is as defined in claim 2, and X is a hydroxy group or a leaving group;

b) reaction of the resulting substrate-bound amide of the formula S-L-A'-N(R^1)-CO-CH_2-CO-R^2 wherein S, L, A', R^1, and R^2 are as defined in claim 2, with a primary amine of the general structure R^3-NH_2 wherein R^3 is as defined in claim 2, in the presence of a dehydrating agent;

c) cyclization of the resulting substrate-bound enamine of the formula S-L-A'-N(R^1)-CO-CH=C(NHR^3)-R^2, by treatment with a sulfonyl azide of the general structure R-SO_2-N_3, wherein R is alkyl, aryl optionally substituted with alkyl or acylamino, in the presence of a base, in order to prepare a compound of formula II,

d) subjection of the resulting substrate-bound compound of formula II to cleavage conditions in order to prepare the compound of formula I.

4. The method according to claim 3 further comprising the step of screening the final product of formula I directly against a specific receptor or enzyme.

5. A method for preparing a compound according to claim 2 comprising the steps of:

a) acylation of a substrate-bound free primary or secondary amine of the formula S-L-A'-N(R^1)H, wherein S, L, A' and R^1 are as defined in claim 2, with a 3-oxoalkanoic acid derivative of the general structure R^2-CO-CH_2-COX, wherein R^2 is as defined in claim 1, and X is a hydroxy group or a leaving group;

b) reaction of the resulting substrate-bound amide of the formula S-L-A'-N(R^1)-CO-CH_2-CO-R^2 wherein S, L, A', R^1, and R^2 are as defined in claim 2, with a primary amine of the general structure R^3-NH_2 wherein R^3 is as defined in claim 2, in the presence of a dehydrating agent;

c) cyclization of the resulting substrate-bound enamine S-L-A'-N(R^1)-CO-CH=C(NHR^3)-R^2, by treatment with a sulfonyl azide of the general structure R-SO_2-N_3, wherein R is alkyl, aryl optionally substituted with alkyl or acylamino, in the presence of a base, in order to prepare a compound of formula II.

6. The method according to claim 5 further comprising the step of screening the final product of formula II directly against a specific receptor or enzyme.

7. The method according to any one of the claims 3, 4, 5 or 6 wherein step a) initially comprises the step of:

attachment of a compound having a free or protected primary or secondary amino group of the formula A-NH-R^1 to a substrate, optionally followed by a deprotection step, in order to generate a substrate-bound free primary or secondary amine of the formula S-L-A'-N(R^1)H, wherein S, L, A' and R^1 are as defined in claim 2.

8. The method according to claim 7 wherein said compound having a free or protected primary or secondary amino group is first coupled to a linker whereafter said linker is attached to said substrate.

9. The method according to claim 7 wherein said substrate is first attached to said linker whereafter said compound having a free or protected primary or secondary amino group is coupled to said linker.

10. The method according to any one of the preceding method claims wherein the sulfonyl azide is *p*-toluenesulfonyl azide and the base is diisopropylethylamine.

11. The method according to any one of the preceding method claims wherein the 3-oxoalkanoic acid derivative is 3-oxobutyric acid phenyl ester or 3-oxobutyric acid 4-nitrophenyl ester.

12. An array comprising m different compounds of formula I, at selected known positions in m containers, wherein m is an integer equal to or greater than 2.

13. An array comprising m different compounds of formula II, wherein m is an integer equal to or greater than 2, at selected known positions on one or more substrates.

14. The array according to claim 12 or 13, wherein m is between 60 to 100, preferably 80.

15. An array comprising one compound of formula I or n different compounds of formula I, wherein n is an integer equal to or greater than 2, at selected known positions in m containers, or at selected known positions on a substrate, and one compound of formula II or m-n different compounds of formula II, wherein m is an

integer equal to or greater than 2, and m>n, at selected known positions on one or more substrates.

16. The array according to claim 15, wherein m is between 60 to 100, preferably 80.

17. An array comprising p different mixtures of compounds of formula I, at selected known positions in p containers, wherein p is an integer equal to or greater than 2.

18. An array comprising p different mixtures of compounds of formula II wherein p is an integer equal to or greater than 2, at selected known positions on one or more substrates.

19. The array according to claim 17 or 18, wherein p is between 60 to 100, preferably 80.

20. An array comprising one mixture of compounds of formula I or r different mixtures of compounds of formula I, wherein r is an integer equal to or greater than 2, at selected known positions in p containers, or at selected known positions on a substrate, and one mixture of compounds of formula II, or p-r different mixtures of compounds of formula II, wherein p is an integer equal to or greater than 2, and p>r, at selected known positions on one or more substrates.

21. The array according to claim 20, wherein p is between 60 to 100, preferably 80.

22. A method for preparing the array according to claim 13 or 14 comprising, carrying out at selected known positions on one or more substrate(s) the steps of:

a) simultaneous acylation of each and every single substrate-bound free primary or secondary amine of the formula S-L-A'-N(R^1)H, wherein S, L, A' and R^1 are as defined in claim 2, with a 3-oxoalkanoic acid derivative of the general structure R^2-CO-CH_2-COX, wherein R^2 is as defined in claim 2, and X is a hydroxy group or a leaving group;

b) reaction of each and every one of the resulting substrate-bound amides of the formula S-L-A'-N(R^1)-CO-CH_2-CO-R^2 wherein S, L, A', R^1, and R^2 are as defined in claim 2, with a primary amine of the general structure R^3-NH_2 wherein R^3 is as defined in claim 2, in the presence of a dehydrating agent;

c) cyclization of each and every one of the resulting substrate-bound enamines of the formula S-L-A'-N(R^1)-CO-CH=C(NHR^3)-R^2, by treating each and every one of said enamines with a sulfonyl azide of the general structure R-SO_2-N_3, wherein R is alkyl, aryl optionally substituted with alkyl or acylamino, in the presence of a base, in order to prepare m compounds of formula II, attached to one or more substrate(s).

23. A method for preparing the array according to claim 12 or 14, the method of claim 22 further comprising the step of:

d) subjection of the resulting m substrate-bound compounds of formula II to cleavage conditions in order to prepare m compounds of formula I, at selected known positions in m containers, wherein m is an integer equal to or greater than 2.

24. A method for preparing the array according to claim 15 or 16, the method of claim 22 further comprising the step of:

d) subjection of the resulting m substrate-bound compounds of formula II to cleavage conditions in order to prepare n compounds of formula I, and m-n compounds of formula II, at selected known positions in m containers, or at selected known positions on a substrate.

25. The method according to any one of the claims 22, 23, or 24 wherein step a) initially comprises the step of:

attachment of m compounds having a free or protected primary or secondary amino group of the formula A-NH-R^1 to one or more substrate(s), at selected known positions on said one or more substrate(s), optionally followed by a deprotection step, in order to generate m substrate-bound free primary or secondary amines of the formula S-L-A'-N(R^1)H, wherein S, L, A' and R^1 are as defined in claim 2.

26. The method according to claim 25 wherein said compound having a free or protected primary or secondary amino group is first coupled to a linker whereafter said linker is attached to said substrate.

27. The method according to claim 25 wherein said substrate is first attached to said linker whereafter said compound having a free or protected primary or secondary amino group is coupled to said linker.

28. The method according to any one of the claims 22, 23, 24, 25, 26, or 27 wherein the sulfonyl azide is *p*-toluenesulfonyl azide and the base is diisopropylethylamine.

29. The method according to any one of the claims 22, 23, 24, 25, 26, 27 or 28 wherein the 3-oxoalkanoic acid derivative is 3-oxobutyric acid phenyl ester or 3-oxobutyric acid 4-nitrophenyl ester.

30. The method according to any one of the claims 22, 23, 24, 25, 26, 27, 28, or 29 further comprising screening the final products directly against a specific receptor or enzyme.

31. The array of compounds of the formula I, according to claim 12 or 14 wherein

R^1 is hydrogen, methyl, ethyl, $CH(CH_2OH)C_2H_3$ or benzyl; or
R^1 and R^5 may be covalently linked to each other, $-R^1-R^5-$ being ethylene, propylene, 2-acetoxypropylene, 2-hydroxypropylene or $-CH(CH_3)CH_2-$.

32. The array of compounds of the formula I, according to any one of the claims 12, 14 or 31 wherein

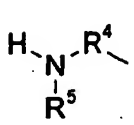
R^2 is methyl or phenyl.

33. The array of compounds of the formula I, according to any one of the claims 12, 14, 31 or 32 wherein

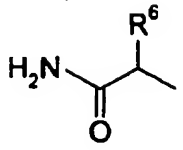
R^3 is alkyl optionally substituted with aryl, heteroaryl, alkoxy, aryloxy, cyano, hydroxy, dialkylamino, arylalkylamino, diarylamino or halogen.

34. The array of compounds of the formula I, according to any one of the claims 12, 14, 31, 32 or 33 wherein

A is a group of formula



or



wherein

R^4 is $-(CH_2)_{n'}-$, wherein n' is 2-5, $-CH_2$-(m-phenylene)-CH_2-, $-CH_2-CH=CH-CH_2-$, $-CH_2-CH(OH)-CH_2-$, $-CH(CH_3)CH_2-$ and 1,2-cyclohexylene;

R^5 is hydrogen, methyl, ethyl, $CH(CH_2OH)C_2H_3$ or benzyl;

R^6 is alkyl, benzyl, (4-hydroxyphenyl)methyl, hydroxymethyl, 2-naphthylmethyl, (3-indolyl)methyl, 4-aminobutyl, (4-imidazolyl)methyl and (2-methylmercapto)ethyl; or

R^6 may be covalently linked to R^1, $-R^6-R^1-$ being $-(CH_2)_3-$.

35. Use of an array according to any one of the claims 12, 13, 14, 15, 16, 17, 18, 19, 20 or 21 for screening compounds of formula I against specific receptors or enzymes.

36. The compound according to claim 1, wherein the compounds of formula I are selected from the group consisting of:

[1-(4-methoxybenzyl)-5-methyl-1H-1,2,3-triazol-4-yl]piperazin-1-ylmethanone trifluoroacetate,
{1-[2-(4-nitrophenyl)ethyl]-5-methyl-1H-1,2,3-triazol-4-yl}piperazin-1-ylmethanone trifluoroacetate,
[5-methyl-1-(3-pyrrolidin-1-yl)propyl-1H-1,2,3-triazol-4-yl]piperazin-1-ylmethanone trifluoroacetate,
[1-(4-hydroxybutyl)-5-methyl-1H-1,2,3-triazol-4-yl]piperazin-1-ylmethanone trifluoroacetate,

{1-[2-(2-hydroxymethyl)phenylthiobenzyl]-5-methyl-1H-1,2,3-triazol-4-yl]piperazin-1-ylmethanone trifluoroacetate,

[5-methyl-1-(3-imidazol-1-yl)propyl-1H-1,2,3-triazol-4-yl]piperazin-1-ylmethanone trifluoroacetate,

[5-methyl-1-(propyn-3-yl)-1H-1,2,3-triazol-4-yl]piperazin-1-ylmethanone trifluoroacetate,

(1-benzyl-5-methyl-1H-1,2,3-triazol-4-yl)piperazin-1-ylmethanone trifluoroacetate,

(1-cyclohexyl-5-methyl-1H-1,2,3-triazol-4-yl)piperazin-1-ylmethanone trifluoroacetate,

(1-benzyl-5-methyl-1H-1,2,3-triazol-4-yl)-1,4-diazepan-1-ylmethanone trifluoroacetate,

{1-[2-(4-nitrophenyl)ethyl]-5-methyl-1H-1,2,3-triazole-4-carboxylic acid N-benzyl-N-(2-benzylamino)ethylamide trifluoroacetate.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 97/00174

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07D 249/04, A61K 31/41
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS-ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0114347 A2 (CIBA-GEIGY AG), 1 August 1984 (01.08.84), see example 17 and 18 --	1
X	EP 0199262 A2 (CIBA-GEIGY AG), 29 October 1986 (29.10.86), see example 16 --	1
X	EP 0229011 A1 (CIBA-GEIGY AG), 15 July 1987 (15.07.87), see example 10 --	1
A	Chimia, Volume 48, 1994, Eduard R. Felder, "The Challenge of Preparing and Testing Combinatorial Compound Libraries in the Fast Lane, at the Front End of Drug Development" page 531 - page 541 --	1-36

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
31 July 1997	02 -08- 1997
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Göran Karlsson Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 97/00174

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Current Opinion in Biotechnology, Volume 6, 1995, Eric M Gordon, "Libraries of non-polymeric organic molecules" page 624 - page 631 --	1-36
A	Angew. Chem. Int. Ed., Volume 35, 1996, Jörg S. Früchtel et al, "Organic Chemistry on Solid Supports" page 17 - page 42 --	1-36

INTERNATIONAL SEARCH REPORT

Information on patent family members

01/07/97

International application No.
PCT/DK 97/00174

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		US 4789680 A	06/12/88
EP 0199262 A2	29/10/86	SE 0199262 T3	
		AU 599024 B	12/07/90
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		CY 1751 A	03/06/94
		DK 169720 B	23/01/95
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		IE 58472 B	22/09/93
		JP 1848050 C	07/06/94
		JP 61243068 A	29/10/86
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		JP 62158264 A	14/07/87